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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY AND LARDNER LLP SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			EXAMINER MERTZ, PREMA MARIA	
			ART UNIT 1646	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/554,407

Applicant(s)

OKUDA ET AL.

Examiner

Prema M. Mertz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 and 55-80 is/are pending in the application.
- 4a) Of the above claim(s) 1-27, 57 and 59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 55, 56, 58 and 60-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/24/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II (claims 55-56, 58, 60-80, species of disease: rheumatoid arthritis) in the in the reply filed on 9/7/05 is acknowledged.

Claims 1-27, 57, 59, are withdrawn from further consideration pursuant to 37 CFR

1.142(b) as being drawn to a nonelected invention.

Claim rejections-35 USC § 112, written description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 64, 65, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The hybridoma cell lines recited on page 16 are essential to the claimed invention. The reproduction of antibodies from the disclosed hybridoma is an extremely unpredictable event. The hybridoma with accession number FERM BP-2998, disclosed on page 16, lines 2-10, of the specification, for example, must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the hybridoma, and it is not apparent if the hybridoma is readily available to the public. If the deposits have been made under the terms of the Budapest

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Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridomas have been deposited under the Budapest Treaty and that the hybridomas will be irrevocably and without restriction or condition be released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridomas described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

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Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 CFR 1.801-1.809 for further information concerning deposit practice.

2b. Claims 55-56, 58, 60-80, are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for a method for treating rheumatoid arthritis comprising administering an IL-6 receptor antibody and an immunosuppressant, wherein the antibody used is a monoclonal antibody PM-1 or MR16-1 or a humanized antibody to human IL-6 receptor, MRA, does not reasonably provide enablement for a method for treating an IL-6 related disease, comprising administering an IL-6 antagonist and an immunosuppressant to a patient requiring such a treatment or a method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related diseases, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such a treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification delimits the instant method to administering antibodies PM-1, MR16-1 or MRA, however, claims 55 and 56 recite a method for treating an IL-6 related disease, comprising administering an IL-6 antagonist and an immunosuppressant to a patient requiring such a treatment and a method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related diseases, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such a treatment, respectively. With respect to these claims, as recited, what is claimed in the instant invention broadly encompasses a method of administering "all" IL-6 antagonists. While the specification discloses that a "IL-6 antagonist" (see page 3,

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lines 25-30) is “preferably” an anti-IL-6R antibody and this is the biological property which the administered compound is expected to exhibit, the specification is non-enabling for the unlimited number of compositions comprising “an IL-6 antagonist”, and which are encompassed by the scope of the claims. Claim 55, for example, is a single means claim (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts have held that: “A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph.” (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for the IL-6 antagonist have been recited in the claim and only a biological activity has been recited, the claim encompasses every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. Therefore, not only proteins, such as IL-6 antagonist peptides but antibodies against IL-6 and antibodies against the IL-6R, which exhibit an antagonist activity are encompassed by the scope of the claims. The claimed invention encompasses a method of administering compositions not envisioned or described in the specification, and neither does the specification disclose how these claimed compositions can be distinguished from each other. The specification only enables treating rheumatoid arthritis by administering MRA, PM-1 or MR16-1 antibodies, the antibodies having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known proteins. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1)

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quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which other IL-6 antagonists to be administered are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the methods taught in the specification unpredictable (see pages 30-32). Therefore, it would require undue experimentation to determine which IL-6 antagonists to be administered in the claimed method would be encompassed by the scope of the claims. The disclosure of the three IL-6 receptor antibodies, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims, which encompass every and all IL-6 antagonist. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological

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activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable compositions in the claimed method, may be innumerable, and the enabled embodiments amount to only three. Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe treatment of a disease other than rheumatoid arthritis by administering PM-1, MR16-1 and MRA antibodies, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. It is suggested that by employing conventional claim language, the claims be amended to include the specific antibodies supported by the instant specification in the claimed method.

Claim rejections-35 U.S.C. 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 55-56, 58, 60-80, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 is vague and indefinite for several reasons.

Claim 55, line 1, is vague and indefinite because it recites "an IL-6 related disease". The metes and bounds of the claim are unclear because it is unclear which of the numerous known and unknown diseases claimed involve IL-6.

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Claim 55, line 2, is vague and indefinite because it recites “an IL-6 antagonist”. The metes and bounds of the claim are unclear because it is unclear which of the numerous IL-6 antagonists claimed can be used in the treatment of the unknown disease.

Claim 56 is vague and indefinite for several reasons.

Claim 56, line 2, is vague and indefinite because it recites “IL-6 related diseases”. The metes and bounds of the claim are unclear because it is unclear which of the numerous known and unknown diseases claimed involve IL-6.

Claim 56, lines 1 and 3, is vague and indefinite because it recites “an IL-6 antagonist”. The metes and bounds of the claim are unclear because it is unclear which of the numerous IL-6 antagonists claimed can be used in the treatment of the unknown disease.

Claim 58, line 1, is vague and indefinite because it recites “an IL-6 related disease”. The metes and bounds of the claim are unclear because it is unclear which of the numerous known and unknown diseases claimed involve IL-6.

Claims 60-80, are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

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subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4a. Claims 55, 56, 68, are rejected under 35 U.S.C. 102(b) as being anticipated by U.S.

Patent No. 5,210,075 ('075 patent).

This patent teaches a method of treating an IL-6 mediated disease such as rheumatoid arthritis by administering an IL-6 antagonist peptide in combination with an immunosuppressant (see column 23, lines 1-4; column 29, lines 46-48). Thus the '075 patent anticipates instant claims 55, 56, 68.

4b. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No.

5,888,510 ('510 patent).

The '510 patent teaches a method of treating an IL-6 mediated disease such as rheumatoid arthritis by administering an IL-6 receptor antibody (see column 13-14, Example 2; column 14, claims 6-11). Thus the '510 patent anticipates instant claim 58.

4c. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Nishimoto et al (2002).

The reference teaches a method of treating an IL-6 mediated disease, rheumatoid arthritis, by administering an IL-6 receptor antibody. Thus the reference anticipates instant claim 58.

4d. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by EP 1074268 (2001).

The reference teaches a method of treating ulcerative colitis by administering IL-6 receptor antibodies PM-1 and MR16-1 to be administered between doses 0.01 and 100 mg/kg for the treatment of ulcerative colitis or Crohn's disease (see paragraph [0017], [0034]). Thus the reference anticipates instant claim 58.

4e. Claims 55, 56, are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/10338 (1997).

The reference teaches a method of treating sepsis by combination therapy with IL-6 receptor antagonists (IL-6 muteins) and anti-TNF antibodies (immunosuppressants according to the instant specification page 7, line 5). Thus the reference anticipates instant claims 55, 56.

4f. Claims 55, 56, are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/64070 (1999).

The reference teaches a method of treating sepsis by combination therapy with IL-6 receptor antagonists (IL-6 muteins) and anti-TNF antibodies (immunosuppressants according to the instant specification page 7, line 5). Thus the reference anticipates instant claims 55, 56.

4g. Claims 55, 56, 58, 60, 61, 68, are rejected under 35 U.S.C. 102(b) as being anticipated by Choy et al (2002).

The reference teaches a method of treatment of rheumatoid arthritis by using an anti-IL-6 receptor antibody (MRA) (page 3143). One group of patients receives a dose of 1.0 mg/kg of MRA and the patients were allowed to take prednisolone at a daily dose inferior to 7.5 mg (see

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page 3144, column 2, Patients and Methods, first full paragraph). Therefore the reference anticipates the subject-matter of claims 55, 56, 58, 60, 61, 68.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5a. Claims 55, 56, 58, 60, 61, 62, 63, 68-80, are rejected under 35 U.S.C. 103(a) as unpatentable over Choy et al (2992).

The reference teaches a method of treatment of rheumatoid arthritis by using an anti-IL-6 receptor antibody (MRA) (see page 3143). One group of patients receives a dose of 1.0 mg/kg of MRA and the patients were allowed to take prednisolone at a daily dose inferior to 7.5 mg (see page 3144, column 2, Patients and Methods, first full paragraph). The reference does not disclose

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whether the MRA antibody is administered simultaneously with the prednisolone and does not teach administering methotrexate (MTX) as an immunosuppressant.

It would be obvious to one of ordinary skill in the art to substitute and administer the immunosuppressant, methotrexate in the method disclosed by Choy et al. One of ordinary skill in the art would have been motivated to do so because the Choy reference teaches that concomitant oral steroid treatment of prednisolone was permitted in the method of Choy et al (see page 3144, column 2, Patients and Methods, first full paragraph, last 7 lines). Thus the artisan would have expected equal success using methotrexate. Furthermore, one of skill in the art would have been motivated to adjust the dosage of the IL-6R antibody to determine the dosage which has the maximum effect at the minimum dosage for highest efficiency. As the administration schedule of the anti IL6-R antibody and the immuno-suppressant does not have any surprising effect, the subject-matter of claims 55, 56, 58, 60, 61, 62, 63, 66, 68-80, is rendered obvious by the reference.

5b. 55, 56, 58, 60, 61, 62, 63, 66, 68-80, are rejected under 35 U.S.C. 103(a) as unpatentable over Choy et al (2992) in view in of Queen et al. (U.S. Patent No. 5,530,101).

The disclosure of Choy et al has been set forth above (see paragraph 5a above). However, Choy et al does not disclose administering humanized antibodies to IL-6R. Queen et al., (column 13, lines 5-65) teaches the humanization of monoclonal antibodies, as well as the issues involved in designing a humanized antibody that retains high affinity for its antigen. Queen et al., (column 17, lines 31-43) further teaches the production of antibody fragments, including the Fab fragment.

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Therefore, at the time the invention was made, it would have been prima facie obvious to a person of ordinary skill in the art to obtain humanized antibodies as taught by Queen et al, to the IL-6R protein as taught by Choy et al. The motivation for doing so would have been the decreased immunogenicity of humanized antibodies when injected into humans, while the humanized antibodies retain their affinity for their epitope (Queen et al., (column 2, lines 5-8)).

Conclusion

No claim is allowed.

Claims 55-56, 58, 60-80, are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz Ph.D., J.D.
Primary Examiner
Art Unit 1646
September 24, 2007